Exhibit D

UNITED STATES v.
GREGORY ABBOTT AND MARCIA ABBOTT,
19-cr-10117-1 (D. Mass.)

Articles in Support of Gregory and Marcia Abbott

1

CDC Centers for Disease Control and Prevention

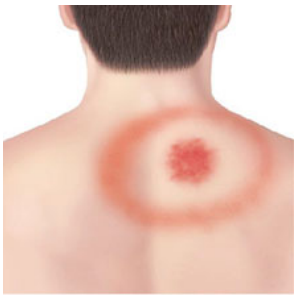
Lyme Disease

Signs and Symptoms of Untreated Lyme Disease

Seek medical attention if you observe any of these symptoms and have had a tick bite, live in an area known for Lyme disease, or have recently traveled to an area where Lyme disease occurs.

Untreated Lyme disease can produce a wide range of symptoms, depending on the stage of infection. These include fever, rash, facial paralysis, and arthritis.

Early Signs and Symptoms (3 to 30 Days After Tick Bite)

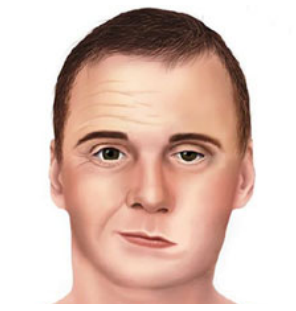


"Classic" Erythema Migrans Rash

- Fever, chills, headache, fatigue, muscle and joint aches, and swollen lymph nodes may occur in the absence of rash
- Erythema migrans (EM) rash (see photos):
  - Occurs in approximately 70 to 80 percent of infected persons
  - Begins at the site of a tick bite after a delay of 3 to 30 days (average is about 7 days)
  - Expands gradually over several days reaching up to 12 inches or more (30 cm) across
  - May feel warm to the touch but is rarely itchy or painful
  - Sometimes clears as it enlarges, resulting in a target or “bull’s-eye” appearance
  - May appear on any area of the body

Later Signs and Symptoms (days to months after tick bite)

Swollen Knee



- Severe headaches and neck stiffness
- Additional EM rashes on other areas of the body
- Facial palsy (loss of muscle tone or droop on one or both sides of the face)
- Arthritis with severe joint pain and swelling, particularly the knees and other large joints.
- Intermittent pain in tendons, muscles, joints, and bones
- Heart palpitations or an irregular heart beat (Lyme carditis)
- Episodes of dizziness or shortness of breath
- Inflammation of the brain and spinal cord
- Nerve pain
- Shooting pains, numbness, or tingling in the hands or feet

Facial Palsy

More about rashes

- A small bump or redness at the site of a tick bite that occurs immediately and resembles a mosquito bite, is common. This irritation generally goes away in 1-2 days and is not a sign of Lyme disease.
- A rash with a very similar appearance to EM occurs with Southern Tick-associated Rash Illness (STARI), but is not Lyme disease
- Ticks can spread other organisms that may cause a different type of rash.

Diagnosis & Testing

Treatment

Page last reviewed: August 15, 2019

2

CHRONIC NEUROLOGIC MANIFESTATIONS OF LYME DISEASE

ERIC L. LOGIGIAN, M.D., RICHARD F. KAPLAN, PH.D., AND ALLEN C. STEERE, M.D.

Abstract *Background and Methods.* Lyme disease, caused by the tick-borne spirochete *Borrelia burgdorferi,* is associated with a wide variety of neurologic manifestations. To define further the chronic neurologic abnormalities of Lyme disease, we studied 27 patients (age range, 25 to 72 years) with previous signs of Lyme disease, current evidence of immunity to *B. burgdorferi,* and chronic neurologic symptoms with no other identifiable cause. Eight of the patients had been followed prospectively for 8 to 12 years after the onset of infection.

Results. Of the 27 patients, 24 (89 percent) had a mild encephalopathy that began 1 month to 14 years after the onset of the disease and was characterized by memory loss, mood changes, or sleep disturbance. Of the 24 patients, 14 had memory impairment on neuropsychological tests, and 18 had increased cerebrospinal fluid protein levels, evidence of intrathecal production of antibody to *B. burgdorferi,* or both. Nineteen of the 27 patients (70 percent) had polyneuropathy with radicular pain or distal paresthesias; all but two of these patients also had encephalopathy. In 16 patients electrophysiologic testing showed an axonal polyneuropathy. One patient had leukoencephalitis with asymmetric spastic diplegia, periventricular white-matter lesions, and intrathecal production of antibody to *B. burgdorferi.* Among the 27 patients, associated symptoms included fatigue (74 percent), headache (48 percent), arthritis (37 percent), and hearing loss (15 percent). At the time of examination, chronic neurologic abnormalities had been present from 3 months to 14 years, usually with little progression. Six months after a two-week course of intravenous ceftriaxone (2 g daily), 17 patients (63 percent) had improvement, 6 (22 percent) had improvement but then relapsed, and 4 (15 percent) had no change in their condition.

Conclusions. Months to years after the initial infection with *B. burgdorferi,* patients with Lyme disease may have chronic encephalopathy, polyneuropathy, or less commonly, leukoencephalitis. These chronic neurologic abnormalities usually improve with antibiotic therapy. (N Engl J Med 1990; 323:1438-44.)

LYME disease, which is caused by the tick-borne spirochete *Borrelia burgdorferi,* is associated with a wide variety of neurologic abnormalities.[1-7] Early in the illness, many patients have episodes of headache and mild meningism.[8] Within several weeks, about 15 percent have objective neurologic abnormalities, most commonly lymphocytic meningitis, motor or sensory radiculoneuritis, or cranial neuropathy, particularly facial palsy.[2,3] A similar syndrome of meningoradiculitis occurs in Europe.[4,9,10] These early neurologic abnormalities can be cured with antibiotic therapy,[11,12] and even if untreated, they usually resolve within months.[4]

Chronic neurologic involvement, affecting either the central or peripheral nervous system, may also occur in Lyme borreliosis. In Germany, Ackermann et al. described 44 patients with progressive borrelial encephalomyelitis, a severe neurologic disorder characterized by spastic paraparesis or tetraparesis, ataxia, cognitive impairment, bladder dysfunction, and cranial neuropathy, particularly deficits of the seventh or eighth cranial nerve.[5] In all cases, the diagnosis was proved by the demonstration of intrathecal production of IgG antibody to *B. burgdorferi.* In addition, acrodermatitis chronica atrophicans, a late skin manifestation of Lyme borreliosis reported primarily in Europe, has been associated with a sensory polyneuropathy[13,14] and with mental disturbances.[15]

In the United States, Halperin et al. described two chronic neurologic syndromes associated with Lyme disease: one involved the peripheral nervous system and was characterized by paresthesias and electrophysiologic evidence of axonal polyneuropathy,[6] and the other involved the central nervous system and was manifested by encephalopathy with memory impairment.[7] The patients with central nervous system involvement usually had intrathecal production of antibodies to the spirochete, but those with abnormalities of the peripheral nervous system did not. A few patients have been described with other neurologic abnormalities thought to be due to Lyme disease, including encephalitis,[16-18] dementia,[18,19] psychiatric syndromes,[17] possible demyelinating disease,[17,19] stroke,[20,21] brain-stem abnormalities,[17] and extrapyramidal syndromes.[22] In some instances, however, the evidence linking these syndromes to infection with *B. burgdorferi* was incomplete.

The goal of the current study was to define further the chronic neurologic abnormalities of Lyme disease. We describe the clinical courses, diagnostic studies, and treatment responses of 27 patients in whom chronic neurologic syndromes developed months to years after the onset of Lyme disease.

METHODS

Neurologic Evaluation

From October 1987 through December 1989, we evaluated a total of 37 patients with chronic neurologic symptoms following well-recognized manifestations of Lyme disease. Eight of them had been entered previously into clinical studies of Lyme disease and had been followed prospectively for 8 to 12 years after the onset of infection. The 37 patients had detailed neurologic evaluations, including lumbar puncture, neuropsychological testing, electrophysiologic studies, and magnetic resonance imaging of the head. The antibody responses to *B. burgdorferi* in serum were determined by indirect enzyme-linked immunosorbent assay[23] and in serum and cerebrospinal fluid samples obtained simultaneously, by capture enzyme immunoassay.[24] If the patient was seronegative according to these methods, the serum was further tested by immunoblotting,[25] and peripheral-blood mononuclear cells were tested for reactivity with borrelial antigens by proliferative assay.[26]

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Neuropsychological tests were selected to provide measures of immediate and delayed memory, conceptualization, copying, perceptual discrimination, and language. These tests included the Wechsler Memory Scales, California Verbal Learning Test, Wisconsin Card-Sorting Test, Trailmaking Test, Rey–Osterrieth Complex Figure Test, Finger-Tapping Test, Benton Face-Discrimination Test, Hooper Visual Organization Test, Boston Naming Test, Token Test, and Oral Word-Association Test. In addition, intelligence quotient was estimated with either the Wechsler Adult Intelligence Scale–Revised or the Shipley Hartford Institute of Living Scale. Finally, symptoms of concurrent psychopathology, such as depression, were assessed by the Minnesota Multiphasic Personality Inventory. The test scores were transformed into standard scores that were calculated from published, age-corrected normative data. According to a previously described system,[27] evidence of memory impairment was defined as scores that were 2 SD below the normative mean on any one of the three tests of memory (Wechsler Memory Scales, California Verbal Learning Test, or Rey–Osterrieth Complex Figure Test) or more than 1 SD below the mean on two of the tests. A score of 70 or above on the Minnesota Multiphasic Personality Inventory was considered indicative of depression.

A detailed electromyographic examination of limb and paraspinal muscles was performed with concentric needle electrodes. Motor-nerve and sensory-nerve conduction studies of the median, ulnar, peroneal, and tibial nerves were performed with 10-mm surface recording and stimulating electrodes. For magnetic resonance imaging of the brain, T_1-weighted sagittal and axial images were obtained on a 1.0-tesla Siemens Magnetom with a repetition time to echo time of 650/20 msec, and T_2-weighted axial images were obtained with a repetition time to echo time of 3000/45 and 90 msec.

Criteria for Case Inclusion

Of the 37 patients, 5 who had memory difficulties, depression, or headache after erythema migrans were excluded because they had normal neurologic tests, negative or indeterminate antibody responses to *B. burgdorferi*, and no reactivity of mononuclear cells to borrelial antigens. Five additional patients who had dementia, demyelinating disease, or headache were excluded because Alzheimer's disease, multiple sclerosis, or brain tumor was the likely diagnosis. Four of these five patients still had antibody responses to *B. burgdorferi*. We believe that the remaining 27 patients had neurologic abnormalities caused by infection with *B. burgdorferi*. All 27 had previously had signs of Lyme disease, had neurologic symptoms lasting at least three months that could not be attributed to another cause, and had current evidence of humoral or cellular immunity to *B. burgdorferi*, as shown by an elevated serum IgG or IgM antibody titer of at least 1:400,[23] five or more IgG antibody bands to spirochetal polypeptides,[25] or a stimulation index of 10 or more in response to borrelial antigens.[26]

Treatment Regimen and Follow-up Examinations

The patients were treated with 2 g of ceftriaxone intravenously once a day for 14 days. Complete blood counts and liver-function tests were done on days 0, 7, and 14 to monitor the effect of therapy. Follow-up examinations were performed three and six months later. Serologic testing for *B. burgdorferi* was repeated at each follow-up visit, and all samples were tested again on a single plate to assess the change in titer. If possible, neurologic tests whose results had been abnormal in the initial examination were repeated at the six-month follow-up examination.

Results

Course of Lyme Disease

Of the 27 patients with chronic neurologic abnormalities due to Lyme disease, 23 (85 percent) had erythema migrans at the beginning of the illness and 2 others (7 percent) had an influenza-like illness without rash during the summer, days to weeks before the onset of early neurologic involvement (Table 1). The two patients who did not have symptoms of early infection did have arthritis followed by neurologic abnormalities. In 11 patients (41 percent), early symptoms included severe headache, mild neck stiffness, or spinal pain. Eight patients (30 percent) had early neurologic abnormalities consisting of facial palsy, sometimes with meningitis or thoracic radiculoneuritis, a median of one month after the onset of erythema migrans. These abnormalities resolved within one to two months except in one patient, who had mild residual facial weakness and a unilateral hearing impairment. A median of six months after the onset of disease, 19 patients (70 percent) began to have brief episodes of arthritis affecting primarily the knees. Arthritis occurred in all these patients before the chronic neurologic symptoms developed, and it was still present in 10 patients (37 percent) when the chronic neurologic abnormalities were noted.

Symptoms of chronic involvement of the peripheral nervous system developed a median of 16 months after the onset of infection, whereas symptoms of central nervous system involvement usually began later, a median of 26 months after the onset of disease (Table

Table 1. Course of Lyme Disease in the 27 Study Patients.*

Median age — yr (range)	49	(25–72)
Male/female	14/13	(52/48)
Early infection	25	(92)
Tick bite	10	(37)
Erythema migrans	23	(85)
Influenza-like summer illness without rash	2	(7)
Headache and neck stiffness or spinal pain	11	(41)
Oral antibiotics for early symptoms		
Doxycycline or tetracycline	4	(15)
Penicillin	2	(7)
Erythromycin	1	(4)
Early neurologic abnormalities	8	(30)
Median time from erythema migrans to early neurologic involvement — mo (range)	1	(0.5–2)
Facial palsy	8	(30)
Meningitis	2	(7)
Radiculoneuritis	1	(4)
Doxycycline for facial palsy	1	(4)
Oligoarticular arthritis	19	(70)
Median time from erythema migrans to arthritis — mo (range)	6	(1–57)
Antibiotics		
Oral tetracycline	1	(4)
Intramuscular penicillin V benzathine	1	(4)
Chronic neurologic abnormalities	27	(100)
Median time from erythema migrans to chronic peripheral nervous system involvement — mo (range)	16	(1–156)
Median time from erythema migrans to chronic central nervous system involvement — mo (range)	26	(1–168)
Duration of chronic neurologic involvement at time of evaluation — mo (range)	12	(3–168)
Intravenous antibiotics for arthritis and neurologic abnormalities		
Penicillin	3	(11)
Ceftriaxone	3	(11)

*Unless otherwise noted, values are numbers of patients, with percentages given in parentheses.

1). At the far end of the spectrum, these abnormalities began 10 or more years after the onset of disease, after long periods of latent infection (Fig. 1). At the time of the current evaluation, chronic neurologic involvement had usually been present for more than 1 year, and in several patients for 10 or more years. Fifteen of the 27 patients (56 percent) had already been treated with one or more courses of antibiotic therapy before this evaluation; in six cases, they had received two-week courses of intravenous penicillin or ceftriaxone.

Chronic Neurologic Abnormalities

Seventeen of the patients (63 percent) had abnormalities of both the central and peripheral nervous systems manifested as subacute encephalopathy and axonal polyneuropathy, seven patients (26 percent) had encephalopathy alone, two (7 percent) had polyneuropathy alone, and the remaining patient (4 percent) had leukoencephalitis.

Subacute Encephalopathy

Of the 27 patients, 24 had a mild encephalopathy. Twenty-two of them had difficulty remembering things (Table 2). They forgot names, missed appointments, or misplaced objects. To compensate, they often made daily lists. Ten patients had symptoms of depression, and three of them sought psychiatric help or received antidepressant medication. Eight patients had excessive daytime sleepiness, and seven had extreme irritability. They became angry over circumstances that previously caused only minor annoyance. Finally, five patients had subtle symptoms of a language disturbance, with difficulty finding words. No one had seizures, myoclonus, or a change in the level of consciousness. Although most patients were able to remain employed, three quit their jobs, three decreased their work hours to part-time, and two retired early.

Table 2. Signs and Symptoms of Chronic Neurologic Abnormalities.

Signs and Symptoms	No. of Patients (%)
Encephalopathy	24 (89)
Memory loss	22 (81)
Depression	10 (37)
Sleep disturbance	8 (30)
Irritability	7 (26)
Difficulty finding words	5 (19)
Polyneuropathy	19 (70)
Spinal or radicular pain	11 (41)
Distal paresthesia	7 (26)
Sensory loss	12 (44)
Lower-motor-neuron weakness	2 (7)
Ankle hyporeflexia	2 (7)
Leukoencephalitis	1 (4)
Upper-motor-neuron weakness	1 (4)
Hyperreflexia	1 (4)
Increased muscle tone	1 (4)
Other symptoms	27 (100)
Fatigue	20 (74)
Headache	13 (48)
Hearing loss	4 (15)
Tinnitus	2 (7)
Fibromyalgia	4 (15)

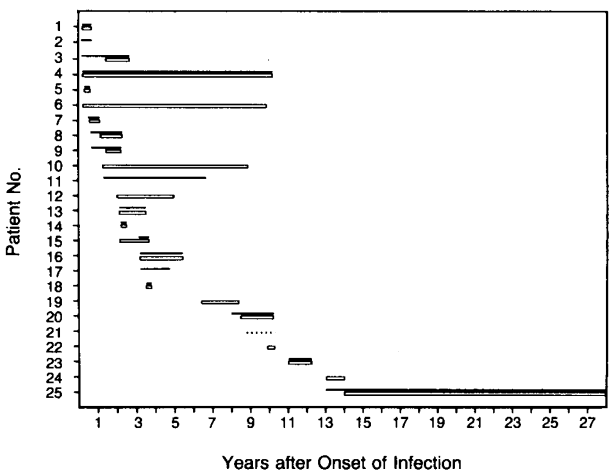

Figure 1. Interval between the Onset of Lyme Disease and the Occurrence of Encephalopathy, Polyneuropathy, or Leukoencephalitis and the Duration of These Complications in the 25 Patients in Whom the Onset of Infection Could Be Determined.

Chronic neurologic abnormalities began 1 month to 14 years after the onset of disease and lasted from 3 months to 14 years.

All 24 patients had at least 12 years of education; they had intelligence quotients that were average or above, and none had a history of neuropsychological impairment. Of the 22 patients with symptoms of memory loss, 12 had evidence of memory impairment on neuropsychological tests, and the 2 with encephalopathy who did not notice any memory changes also had evidence of such impairment on these tests (Table 3). In only six patients was memory dysfunction marked enough to be apparent on neurologic evaluation at the bedside. On the Minnesota Multiphasic Personality Inventory, 9 of the 10 patients with symptoms of depression had scores indicative of depression. Only two patients scored 1 SD below the mean on any other neuropsychological test.

Of the 24 patients with encephalopathy, 21 had elevated serum IgG antibody responses to *B. burgdorferi* (Fig. 2). Of the remaining three patients, all of whom received antibiotic therapy for erythema migrans, one had only an IgM response (1:3200) to the spirochete; one had an IgG response in the indeterminate range (1:200), but the immunoblot showed antibody to six spirochetal polypeptides; and one had only a cellular immune response to borrelial antigens (stimulation index, 28). On analysis of the cerebrospinal fluid, 11 patients (46 percent) had evidence of slight intrathecal production of antibody to *B. burgdorferi:* 8 had only IgG antibody to the spirochete, 1 had both IgG and IgA antibodies, 1 had only IgA antibody, and 1 had only IgM antibody (Fig. 2, Table 3). In addition, 11 patients had increased cerebrospinal fluid protein levels, but only 1 had a pleocytosis of 7 lymphocytes per cubic millimeter. Thus, a total of

Table 3. Results of Neurologic Tests in 27 Patients with Chronic Neurologic Abnormalities.

Test*	Encephalopathy and Polyneuropathy (N = 17)	Encephalopathy Alone (N = 7)	Polyneuropathy Alone (N = 2)	Leukoencephalitis (N = 1)	Total (N = 27)
	number of patients (percent)				
CSF analysis					
Increased protein	8	3	0	1	12 (44)
CSF:serum ratio of antibody to *B. burgdorferi* >1	7	4	0	1	12 (44)
Increased protein or CSF:serum ratio >1	13	5	0	1	19 (70)
Pleocytosis	1	0	0	1	2 (7)
Neuropsychological testing					
Memory loss	12	2	0	1	15 (56)
Depression	6	3	0	0	9 (33)
Electrophysiologic testing					
Abnormal electromyogram	14	0	2	0	16 (59)
Abnormal nerve conduction	7	0	1	0	8 (30)
Magnetic resonance imaging scan of brain					
Small areas of increased T_2-signal intensity	3	1	0	1	5 (19)

*CSF denotes cerebrospinal fluid.

18 patients had increased cerebrospinal fluid protein levels, evidence of intrathecal production of antibody to *B. burgdorferi*, or both. Only one patient had an elevated IgG index and an increased rate of IgG synthesis in cerebrospinal fluid. None of the patients had low glucose levels in cerebrospinal fluid, oligoclonal bands, or a positive Venereal Disease Research Laboratory test. Four of the 24 patients, who were 34, 61, 64, and 72 years of age, had abnormal magnetic resonance imaging scans of the head. They had numerous small, rounded areas of increased T_2-signal intensity, primarily in the peripheral white matter (Fig. 3).

Overall, 23 of the 24 patients had objective evidence of memory impairment, abnormal cerebrospinal fluid findings, or both. Of the 10 patients in whom memory impairment could not be demonstrated on neuropsychological tests, 9 (90 percent) had abnormal cerebrospinal fluid analyses. All four patients with abnormal magnetic resonance imaging scans of the head had objective signs of memory loss, and three of them had abnormal cerebrospinal fluid findings.

Axonal Polyneuropathy

Of the 27 patients, 19 (70 percent) had polyneuropathy; all but 2 of these patients also had encephalopathy. Eighteen of the 19 patients had sensory symptoms: 11 had pain in the cervical, thoracic, or lumbosacral area of the spine, usually accompanied by tingling, burning, spasms, or shooting pain in the limbs or trunk, and 7 had only distal paresthesia, with intermittent tingling or "pins and needles" sensations in the hands or feet (Table 2). On examination, 12 patients had diminished sensation in response to light touch or pinprick within affected cutaneous areas, 2 had ankle hyporeflexia, and 2 had mild weakness of the limbs. The one patient who did not have sensory symptoms had "stocking" sensory loss (affecting the feet and areas of the legs usually covered by stockings) on examination. Sensory signs or symptoms were symmetric in 13 patients and asymmetric in 6.

On electrophysiologic testing, 16 of the 19 patients had evidence of an axonal polyneuropathy (Table 3). Electromyography showed that 9 of the 11 patients with spinal pain and 6 of the 7 patients with only distal symptoms had active or chronic denervation both in proximal paraspinal and in more distal limb muscles. In contrast, only 3 of the 11 patients with spinal pain and 4 of the 7 patients with distal paresthesia had slightly slow conduction velocities of the motor or sensory peroneal and tibial nerves or slightly prolonged motor latencies to the intrinsic muscles of the foot. The single patient with asymptomatic polyneuropathy had slight slowing of conduction velocities in the legs and denervation in the paraspinal and limb muscles. Of the three patients with normal electro-

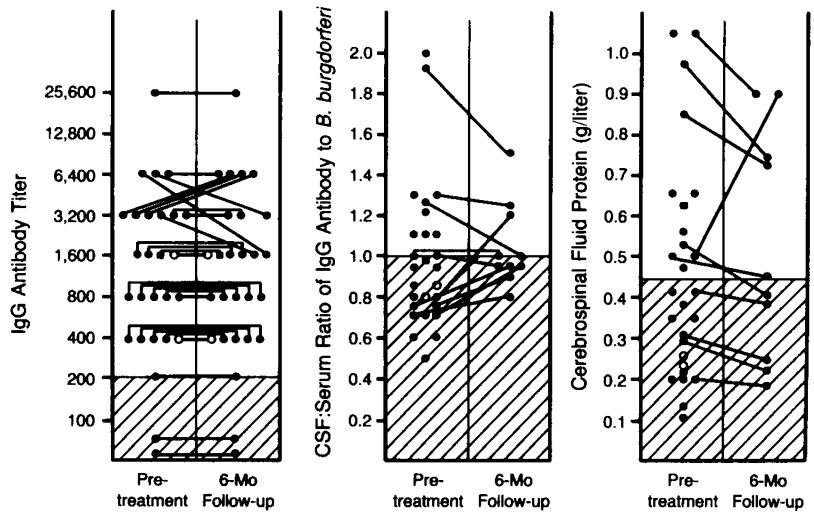

Figure 2. Pretreatment and Follow-up Serum IgG Antibody Responses to *B. burgdorferi*, Cerebrospinal Fluid (CSF):Serum Ratios of IgG Antibody to the Spirochete, and Cerebrospinal Fluid Protein Concentrations in the 27 Patients with Encephalopathy (●), Polyneuropathy Alone (○), or Leukoencephalitis (■). The hatched areas indicate the normal ranges.

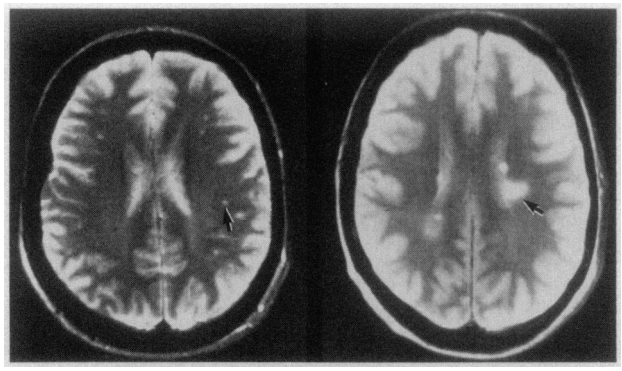

Figure 3. Magnetic Resonance Imaging Scans of the Brain of a 34-Year-Old Woman with Encephalopathy (Left Panel) and a 40-Year-Old Man with Leukoencephalitis (Right Panel).
Arrows indicate peripheral (left panel) and periventricular (right panel) lesions of the white matter.

physiologic studies, two had typical radicular pain and one had distal paresthesia.

Leukoencephalitis

Six years after the onset of Lyme disease, after erythema migrans and several brief attacks of arthritis that were treated with erythromycin and penicillin V benzathine, respectively, 1 of the 24 patients experienced progressive stiffness and then moderate weakness and increased tone in the muscles of his right arm and of both legs. His gait showed reduced arm swing on the right. Tendon jerks were diffusely brisk, with bilateral ankle clonus and Babinski signs. He had urinary urgency and frequency, with occasional episodes of incontinence.

Magnetic resonance imaging of the brain showed numerous small areas of increased T_2-signal intensity in the periventricular regions (Fig. 3). The scan of the spinal cord was normal, as were visual and brain-stem auditory evoked potentials. The serum IgG antibody response to *B. burgdorferi* was 1:12,800. The patient's cerebrospinal fluid showed 6 lymphocytes per cubic millimeter, an increased protein level of 0.64 g per deciliter, a cerebrospinal fluid:serum ratio of IgA antibody to *B. burgdorferi* of 4, and an IgG ratio of 0.98 (Fig. 2, Table 3). Analysis of the cerebrospinal fluid did not show a low glucose level, oligoclonal bands, myelin basic protein, or an increased rate of IgG synthesis. The patient scored 1 SD below the mean on two separate tests of memory. Electrophysiologic studies were normal.

Associated Symptoms

Of the 27 patients, 20 had marked fatigue, which was often a major symptom of their illness. Thirteen patients had mild-to-severe, episodic, non-pounding headache in a global, hemicranial, bifrontotemporal, or occipital distribution. They did not have nausea or visual or somatosensory aura. In two of them, headache was the primary symptom. Four patients, from 35 to 67 years of age, had mild-to-moderate unilateral hearing loss, sometimes accompanied by tinnitus. In all four, the hearing loss was apparent on physical examination, and in the two patients tested, audiometry confirmed a mild, high-frequency, sensorineural hearing loss. During the course of neurologic involvement, four patients had symptoms of fibromyalgia, a chronic pain syndrome associated with tender points in multiple locations, most commonly over spinal or paraspinal areas. However, all four of these patients had abnormal results of cerebrospinal fluid analyses or white-matter lesions on magnetic resonance imaging scans of the brain.

Treatment

The 27 patients were treated with 2 g of intravenous ceftriaxone a day for 14 days. Near the end of therapy, four patients had diarrhea and three had slightly elevated enzyme levels on liver-function tests. At the evaluation six months later, 17 patients (63 percent) were better, including the patient with leukoencephalitis. Improvement often did not begin until several months after the completion of therapy, and recovery was seldom complete. Of the remaining 10 patients, 6 (22 percent) improved but then relapsed, and 4 (15 percent) were no better. The response to treatment among patients with polyneuropathy was slightly better than that among patients with encephalopathy (68 vs. 58 percent).

In general, an improvement in symptoms was accompanied by an improvement in neuropsychological tests (five of six patients) and in nerve-conduction studies (five of seven patients). Regardless of the response to antibiotics, the cerebrospinal fluid protein levels often declined, and the serum and cerebrospinal fluid antibody responses frequently remained the same (Fig. 2). However, the one patient whose cerebrospinal fluid protein levels increased, the one in whom evidence of intrathecal antibody production subsequently developed, and two of the three whose serum antibody titers increased had recurrent symptoms. Although there was objective clinical improvement in the five patients with abnormal magnetic resonance imaging scans of the brain, the lesions showed no change. When pretreatment characteristics were analyzed according to the response to treatment, there was a trend toward a longer duration of infection, higher serum antibody titers, increased cerebrospinal fluid protein levels, and objective evidence of memory impairment in patients who did not respond, but these differences were not statistically significant.

Discussion

In this study of patients with chronic neurologic symptoms following well-recognized manifestations of Lyme disease, three neurologic syndromes emerged: encephalopathy, polyneuropathy, and leukoencephalitis, alone or in combination. These chronic neurologic abnormalities began months to years after the onset

of infection, sometimes after long periods of latency, as in neurosyphilis. In some cases, patients had erythema migrans during the summer followed within weeks by early neurologic abnormalities. Months later, arthritis often dominated the picture, and years later, chronic neurologic involvement became apparent, which often showed little progression for several years. In other cases, however, this chronology was condensed, the system involvement was incomplete or overlapped, chronic neurologic symptoms began early in the illness, or the neurologic abnormalities progressed more rapidly.

The most common form of chronic central nervous system involvement in our patients was subacute encephalopathy affecting memory, mood, and sleep, sometimes with subtle disturbances in language. Diagnosis of this condition may be difficult because the typical symptoms are nonspecific. In addition to evidence of immunity to *B. burgdorferi,* however, most of our patients had memory impairment on neuropsychological tests and abnormal results of cerebrospinal fluid analyses, frequently accompanied by axonal polyneuropathy and arthritis — a clinical picture that is very suggestive of Lyme disease. Although the anatomical and pathological basis for Lyme encephalopathy is not yet known, spirochete-like structures have been seen in brain-biopsy samples from two patients with apparent Lyme encephalitis.[17,28] By analogy with the general-paresis form of neurosyphilis, which may begin with impairment of memory and concentration, irritability, depression, sleep disorder, and fatigue,[29-31] we suspect that the pathologic process of Lyme encephalopathy may be mild, multifocal, and generalized, affecting both the gray and white matter. We excluded three elderly women from our series who had dementia several years after Lyme disease because we could not rule out the diagnosis of Alzheimer's disease. It remains possible that *B. burgdorferi,* like *Treponema pallidum,* may occasionally cause severe cognitive deficits.

In addition to encephalopathy, most of our patients had peripheral sensory symptoms, either distal paresthesias or spinal or radicular pain. Electrophysiologic testing, particularly in those with distal paresthesias, often showed an axonal polyneuropathy, with subtle abnormalities of distal motor-nerve or sensory-nerve conduction. Demyelinating features were not seen. Most of our patients, however, including those with only distal symptoms, also had extensive abnormalities of the proximal nerve segments on electromyography. The pathoanatomical basis for this symmetric or asymmetric polyneuropathy may be mononeuritis multiplex. In support of this idea, sural-nerve biopsies in affected patients have shown predominantly axonal injury with perivascular infiltration of lymphocytes and plasmacytes around epineural vessels.[6,32,33]

One patient in our series had an asymmetric spastic diplegia, upper-motor-neuron bladder dysfunction, subtle memory impairment, pleocytosis, and lesions of the periventricular white matter. This clinical picture is partially compatible with either European borrelial encephalomyelitis[5] or multiple sclerosis. Against the diagnosis of multiple sclerosis was the patient's progressive course involving only the motor system, normal evoked potentials, and the absence of myelin basic protein or oligoclonal bands in cerebrospinal fluid. Most important for the diagnosis of borrelial leukoencephalitis were the findings of lesions of the periventricular white matter and intrathecal production of antibody to *B. burgdorferi.* In two previous studies, patients with classic multiple sclerosis did not have antibody to *B. burgdorferi.*[34,35]

The typical response of our patients to antibiotic therapy supports the role of spirochetal infection in the pathogenesis of each of the syndromes described here. However, our results were not as good as those in previous reports.[6,7] Six months after treatment, more than one third of the patients either had relapsed or were no better. In addition, more than half had previously received antibiotic therapy thought to be appropriate for their stage of disease and still had progression of the illness. The likely reason for relapse is failure to eradicate the spirochete completely with a two-week course of intravenous ceftriaxone therapy. On the other hand, the patients whose conditions did not improve may have had irreversible damage to the nervous system, particularly since the response to therapy tended to be worse in patients with longer durations of disease. This is reminiscent of far-advanced neurosyphilis, in which the response to penicillin may be minimal.[36]

We are indebted to Mr. Bruce Reinhardt, Ms. Karen Weeks, and Ms. Jennifer Whalen for laboratory assistance; to Ms. Linda Vincent and Ms. Mary-Ellen Meadows for assistance with neuropsychological testing; to the neurology residents for their help with patient care; and to Drs. John Halperin and Louis Caplan for their helpful advice.

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CORTICOSTEROIDS AS ADJUNCTIVE THERAPY FOR SEVERE *PNEUMOCYSTIS CARINII* PNEUMONIA IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME

A Double-Blind, Placebo-Controlled Trial

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Abstract *Background.* Preliminary reports suggest that patients with the acquired immunodeficiency syndrome (AIDS) and *Pneumocystis carinii* pneumonia may benefit from the addition of corticosteroid treatment to antibiotic therapy.

Methods. We conducted a double-blind, placebo-controlled trial to assess the efficacy of adjunctive corticosteroids in patients with AIDS and severe *P. carinii* pneumonia. Patients with marked abnormalities in gas exchange who had been treated with antibiotics for less than 72 hours were randomly assigned to receive either methylprednisolone (40 mg) or placebo every 6 hours for 7 days, in addition to treatment for 21 days with trimethoprim–sulfamethoxazole. The primary outcome measures were survival until hospital discharge and the development of respiratory failure.

Results. Twenty-three patients were enrolled in the study; there were no significant differences in base-line clinical or laboratory measures between the two treatment groups. Of 12 patients treated with corticosteroids, 9 (75 percent) survived until hospital discharge, as compared with only 2 of 11 placebo recipients (18 percent) ($P<0.008$). Respiratory failure developed in nine placebo recipients, as compared with only three patients treated with corticosteroids ($P<0.008$). No patient required the interruption or discontinuation of corticosteroid or antibiotic treatment because of toxicity or a complicating event. Because of the marked difference in survival, it was deemed unethical to continue the trial, and the study was terminated.

Conclusions. Early adjunctive corticosteroid therapy can improve survival and decrease the occurrence of respiratory failure in patients with AIDS and severe *P. carinii* pneumonia. (N Engl J Med 1990; 323:1444-50.)

PNEUMOCYSTIS CARINII pneumonia is the most common opportunistic infection associated with the acquired immunodeficiency syndrome (AIDS). In approximately 60 to 65 percent of patients with AIDS, it is the AIDS-defining diagnosis; another 20 percent of such patients acquire the disease over the course of their illness.[1] The death rate from *P. carinii* pneumonia approaches 25 percent, making it a major cause of mortality.[2-4] At present, standard chemotherapy consists of a prolonged course of either trimethoprim–sulfamethoxazole or intravenous pentamidine isethionate (pentamidine).[1,5-10] The predictors of a poor clinical outcome include extensive bilateral pulmonary infiltrates, concurrent pulmonary infections, recurrent *P. carinii* pneumonia, an elevated serum concentration of lactate dehydrogenase, a decreased serum concentration of albumin, a respiratory rate above 30 per

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3

I took all the right meds for Lyme, so why didn't I get better?; We've got to change our thinking about Lyme disease. Here's why.

Washington Post Blogs

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Byline: Mairead Eastin Moloney

Body

In the autumn of 2010, I was a newly minted PhD living in North Carolina and trying to find employment on the elusive tenure track. I juggled my search for a medical sociology position with postdoctoral research, adjunct teaching and a lively social life. My days were full but fulfilling. The first two weeks of November, however, brought leaden fatigue, and I blamed my busy schedule. Seeking respite, I booked an inexpensive silent retreat at a nearby spiritual center.

I lucked into an unusually warm weekend and spent my time strolling well-worn woodland paths and sitting in quiet meditation in a nearby grassy field. Back home after three days, I peeled off my clothes for a shower. Reflected in the bathroom mirror was a rash the shape of a bull's-eye, blooming bright red on my left hip. After dinner I developed a fever that alternately froze and scalded me. My joints turned to piercing shards of glass, and pain stabbed my left temple. My vision blurred and my eyes became so sensitive that I flinched when my husband, Kevin, turned on an overhead light.

A few minutes on Google confirmed that the bull's-eye rash was a clear sign of Lyme disease. I read that antibiotics, administered early, could zap the corkscrew-shaped bacteria and prevent their wreaking long-term havoc on a person's brain, muscles and joints.

But, I learned, antibiotics don't work for everyone.

That night, a Sunday, I snapped a photo of my rash and emailed it to my primary-care physician - let's call him Dr. 1 - who embodied a rare combination of evidence-based brilliance and warm bedside manner. Within the hour, he called in a prescription for 10 days of doxycycline and emailed his administrative assistant to give me his next available appointment.

By Wednesday I was still a bit achy and tired, but I returned to work and canceled my appointment with Dr. 1. The antibiotics seemed to be working their magic.

Two days after swallowing the last peach-colored pill, I was celebrating Thanksgiving with my parents in Atlanta. Standing at my mother's kitchen sink, I noticed that my hip and knee joints throbbed and that I felt cold. When a shattering headache and hazy vision appeared over pumpkin pie, I squeezed Kevin's hand and asked him to take me to the nearest urgent-care provider. There, a physician assistant proposed testing me for Lyme.

"No, thank you," I said. I needed to get home to Dr. 1. As Kevin sped across two states, my fever raged, and I developed palpitations so intense that I worried my heart would give out.

I took all the right meds for Lyme, so why didn't I get better?; We've got to change our thinking about Lyme disease. Here's why.

You're healthy, I reassured myself. You run 10 miles every Sunday. Maybe you just need a longer round of drugs.

Luckily, Dr. 1 could see me the following day.

"Lyme mostly occurs in the northeastern states," he explained as he performed a physical exam. "But we've got something down here called STARI - southern tick-associated rash illness. I suspect that's what you have."

He told me he'd test for Lyme and other tick-borne bacteria.

"My main concern," he added, "is that it might not be Lyme at all. Ten days of antibiotics should have taken care of any tick-borne illness."

I knew that Dr. 1 was quoting me the guidelines of the Infectious Diseases Society of America. But my cursory Internet research had turned up another group, the International Lyme and Associated Diseases Society. This organization recommends that practitioners tailor antibiotic treatments to a patient's symptoms. It also encourages higher-dose antibiotic therapy that extends beyond the disappearance of symptoms.

Which approach was better?

Confused and scared, I asked Dr. 1 for an extended course of antibiotics. He authorized 20 more days, hoping that test results would tell us more.

They did not. I tested negative for Lyme, Rocky Mountain spotted fever and ehrlichiosis - all tick-borne bacterial infections.

Still, I was constantly weary and struggled to concentrate. My ever-present joint pain, headache and fuzzy vision made me feel positively geriatric at age 35.

"You absolutely don't have Lyme," Dr. 1 said at a follow-up visit. "You definitely did have something. The bull's-eye rash was unmistakable. But I still suspect that it was STARI, and there's no test for that."

He opposed further doxycycline. "You probably caught some sort of virus in the midst of this," he said. "Give it a couple of weeks. You'll likely feel better."

But I didn't.

I pored over peer-reviewed journal articles and made inquiries among my social and professional networks. One friend called an infectious-disease specialist she knew on my behalf.

"Does she claim to have post-treatment Lyme disease syndrome?" he asked. "Because people who do are crazy."

On the Internet, I found many tales of prolonged struggles with Lyme disease. Though trajectories and curatives varied, patient success stories had a common denominator: treatment by a Lyme-literate medical doctor, or LLMD. LLMDs appeared to have no formal training or board certification related to tick-borne illnesses. Instead, they were physicians from varying specialties, dedicated to treating patients who might otherwise end up falling through the diagnostic cracks.

My Internet search also turned up Dr. 2, the only LLMD in my town. She practiced allopathic medicine but did not take insurance. She charged $400 for the first visit and $180 for follow-ups. I balked at the cost, but Kevin didn't.

"You've been sick for months," he reminded me.

At my first visit, Dr. 2 suggested two months of antibiotics, double my prior dosage.

Two months? DOUBLE the dose? But I was desperate to regain my health.

"I should warn you," Dr. 2 said, "you'll feel much worse before you feel better. When the bacteria die, they release a toxic gas. It's called a Herxheimer reaction. Your symptoms will intensify, and you'll likely have some new ones. Still, higher and longer doses of antibiotics are the only way to kill these buggers."

At first, the nausea from the higher dose kept me circling the toilet like a wobbly vulture. I also became incredibly photosensitive and developed sun poisoning on my knuckles from an afternoon of driving. I was pummeled by constant pain and fatigue.

"We're killing a lot of bacteria," Dr. 2 told me at my three-month visit. "The fact that you feel so awful tells me that the treatment is working."

"Good," I said. "I guess."

One month later, there was scant evidence of improvement. Dr. 2 added Rifampin to "outsmart" the bacteria. This antibiotic turned my excrement orange, destroyed my appetite and made staying awake for more than a few hours impossible. Still, she added Flagyl, a third antibiotic. I spent the next two days moaning, dry heaving and trembling on the bathroom floor. I called Dr. 2 and pleaded with her to discontinue the Flagyl. Reluctantly, she agreed.

For my next appointment, on a humid June morning, I swathed my shivering frame in fleece and hobbled into Dr. 2's waiting room. Twice, I rushed to the bathroom to retch up burning bile. While Dr. 2 weighed me - I was down from 122 pounds to 108 - I wept.

At the end of that visit, she handed Kevin a sheaf of scripts. There were refills of my two antibiotics and new prescriptions for an anti-nausea drug; a vile powder meant to aid in "detoxification"; an opioid; and an antidepressant. I refused the last two outright.

"Painkillers make me puke," I said. "And I'm not depressed. I'm sick."

For two months I lived in a pain-filled fog, constantly queasy and increasingly weak. I spent most days in bed, a pillow shielding my eyes from the blazing summer sun, comforters piled on my shrinking body.

Somehow, in the midst of my misery, my application for a postdoctoral teaching position at a nearby university was accepted. The new job started in the middle of August, but I was too feeble to climb a flight of stairs or drive a car.

"Please," I begged Dr. 2. "I can't do this anymore."

She wondered whether I would consider disability. I would not. She discontinued everything but the doxycycline.

That fall, buoyed by new-job joy and an increased appetite, I managed to regain nearly 10 pounds and some perspective. Against Dr. 2's advice, I stopped the remaining drug.

Though stronger off the antibiotics, I was not well. At my new job, I found myself reading, rereading and still not comprehending text that I had written myself. At the end of each workday, I'd lock my office door and arrange my aching body on the floor behind my desk. After an hour - sometimes two - of dreamless slumber, I'd stagger out to the nearly empty parking lot and drive carefully home.

A nurse practitioner friend who had witnessed my illness with growing alarm told me about another LLMD. Dr. 3 was board-certified in internal medicine and had nearly four decades of experience. His office was a five-hour drive from my home, and his waiting list nearly three months long. Like Dr. 2, he didn't take insurance.

Dr. 3's initial consult - in January 2012 - lasted half a day. I completed an exhaustive gamut of verbal questions, written surveys, physical and cognitive tests, and blood work. He asserted that peer-reviewed research and tests about Lyme were in their infancy but that he'd had great success treating patients from all over the country.

Kevin and I left that visit $1,800 poorer but with a glimmer of hope.

At our next visit, Dr. 3 guided us through my test results.

The data were mixed. My Lyme test was deemed inconclusive, but I tested positive for two organisms that often co-occur with Lyme. Dr. 3 explained that what we call Lyme is more accurately conceptualized as a complex set of infectious agents passed to a human through the bite of a tick. Many symptoms attributed to Lyme may be the result of co-infections from organisms such as Babesia or Bartonella. These co-infections complicate the illness. Yet these microbiological monsters are rarely considered and can be difficult to detect.

Dr. 3 promised to prescribe only drugs that he felt were absolutely necessary and to take a "go low, go slow" treatment approach. He planned to balance Western medicine with herbal and nutritional supplements.

"It's true that killing the bacteria will make you feel bad, but my job is never to let you get as ill as you did," Dr. 3 said. Allowing patients to suffer constant Herxheimer reactions was counterproductive, he said, perhaps even damaging.

Under Dr. 3's care, I slowly but steadily regained my health. At his urging, I added a range of complementary and alternative health practices. Some were free (mindfulness meditation and exercise), but most were not (copious supplements and regular acupuncture). I'd love to identify a single magic bullet that improved my condition, but I can't. I credit Dr. 3's experience, patient-centered approach, reliance on multiple modes of evidence (such as regular blood work and symptom checks), and a combination of numerous therapies.

I have spent approximately $10,000 a year - roughly a quarter of my pretax postdoc income-on out-of-pocket Lyme-related expenses. Fortunately, Kevin's salary kept us afloat. Many tick-sick patients are not as lucky.

In May 2013, 21/2 years after that odd red rash appeared, Dr. 3 said I could begin tapering off my treatments.

"I recommend that you stay on your immune-boosting supplements for another nine to 12 months," he said. "But you're a different woman than when I met you."

It was true. I had my life back.

In 2014 the Environmental Protection Agency noted that Lyme incidence had doubled since 1991, and the Centers for Disease Control and Prevention revised its annual estimates. In the blink of a mathematical equation, the United States went from 30,000 Lyme cases per year to 300,000.

Improved awareness and surveillance are critical to tackling this public-health problem, as are advances in research and testing. But there's a crisis of practice that must also be addressed, particularly for patients who are diagnosed with late-stage Lyme and for the CDC's estimated 10 to 20 percent of patients who - like me - do not fully recover after standard antibiotic treatment.

Potentially dangerous practitioners such as Dr. 2 thrive in the unregulated Wild West of Lyme care. Meanwhile, clinicians such as Dr. 3 are the medical version of a four-leaf clover. Yet both call themselves LLMDs. Standardization and board certification must be created for this designation.

And Lyme must be redefined, perhaps as a syndrome encompassing a constellation of harmful tick-borne organisms, only some of which are understood.

As anyone who has had a complicated case can attest, Lyme may not kill you, but you'll wish you were dead. Until tick-borne illnesses are treated more seriously, hundreds of thousands of people will experience unnecessary and prolonged suffering.

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I took all the right meds for Lyme, so why didn't I get better?; We've got to change our thinking about Lyme disease. Here's why.

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4

Lyme Disease Is Baffling, Even to Experts

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Meghan O'Rourke September 2019 Issue
Health

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In the fall of 1997, after I graduated from college, I began experiencing what I called “electric shocks”—tiny stabbing sensations that flickered over my legs and arms every morning. They were so extreme that as I walked to work from my East Village basement apartment, I often had to stop on Ninth Street and rub my legs against a parking meter, or else my muscles would begin twitching and spasming. My doctor couldn’t figure out what was wrong—dry skin, he proposed—and eventually the shocks went away. A year later, they returned for a few months, only to go away again just when I couldn’t bear it anymore.

Over the years, the shocks and other strange symptoms—vertigo, fatigue, joint pain, memory problems, tremors—came and went. In 2002, I began waking up every night drenched in sweat, with hives covering my legs. A doctor I consulted thought, based on a test result, that I might have lupus, but I had few other markers of the autoimmune disease. In 2008, when I was 32, doctors identified arthritis in my hips and neck, for which I had surgery and physical therapy. I was also bizarrely exhausted. Nothing was really wrong, the doctors I visited told me; my tests looked fine.

In 2012, I was diagnosed with a relatively mild autoimmune disease, Hashimoto’s thyroiditis. Yet despite eating carefully and sleeping well, I was having difficulty functioning, which didn’t make sense to my doctor—or to me. Recalling basic words was often challenging. Teaching a poetry class at Princeton, I found myself talking to the students about “the season that comes after winter, when flowers grow.” I was in near-constant pain, as I wrote in an essay for *The New Yorker* at the time about living with chronic illness. Yet some part of me thought that perhaps this was what everyone in her mid-30s felt. Pain, exhaustion, a leaden mind.

One chilly December night in 2012, I drove a few colleagues back to Brooklyn after our department holiday party in New Jersey. I looked over at the man sitting next to me—a novelist I’d known for years—and realized that I had no idea who he was. I pondered the problem. I knew I *knew* him, but who was he? It took an hour to recover the information that he was a friend. At home, I asked my partner, Jim, whether he had ever experienced anything like this. He shook his head. Something was wrong.

By the following fall, any outing—to teach my class, or to attend a friend's birthday dinner—could mean days in bed afterward. I hid matters as best I could. Debt piled up as I sought out top-tier physicians (many of whom didn't take insurance)—a neurologist who diagnosed neuropathy of unclear origin, a rheumatologist who diagnosed "unspecified connective-tissue disease" and gave me steroids and intravenous immunoglobulin infusions. I visited acupuncturists and nutritionists. I saw expensive out-of-network "integrative" doctors (M.D.s who take a holistic approach to health) and was diagnosed with overexhaustion and given IV vitamin drips. Many doctors, I could tell, weren't sure what to think. *Is this all in her head?* I felt them wondering. One suggested I see a therapist. "We're all tired," another chided me.

I was a patient of relative privilege who had access to excellent medical care. Even so, I felt terrifyingly alone—until, in the fall of 2013, I found my way to yet another doctor, who had an interest in infectious diseases, and tested me for Lyme. I had grown up on the East Coast, camping and hiking. Over the years, I had pulled many engorged deer ticks off myself. I'd never gotten the classic bull's-eye rash, but this doctor ordered several Lyme-disease tests anyway; though indeterminate, the results led her to think I might have the infection.

I began to do research, and discovered other patients like me, with troubling joint pain and neurological problems. To keep symptoms at bay, some of them had been taking oral and intravenous antibiotics for years, which can be dangerous; one acquaintance of mine was on her fifth or sixth course of IV drugs, because that was the only treatment she'd found that kept her cognitive faculties functioning. I read posts by people who experienced debilitating exhaustion and memory impairment. Some were so disoriented that they had trouble finding their own home. Others were severely depressed. Along the way, nearly all had navigated a medical system that had discredited their testimony and struggled to give them a diagnosis. Many had been shunted by internists to psychiatrists. The stories were not encouraging.

After a decade and a half in the dark, I at last had a possible name for my problems. Yet instead of feeling relief, I felt I had woken into a nightmare. I wasn't sure whether the disease I had really *was* untreated Lyme. Even if I did have Lyme, there was little agreement about how to treat a patient like me—whose test results were equivocal and who had been diagnosed very late in the course of the disease—and no guarantee that I would get better if I tried antibiotics.

It was a scary path to walk down. My own doctor cautioned that the label *Lyme disease* was easy to pin on one's symptoms, because the tests can be inaccurate. I understood. I'd gotten my hopes up before. My experience of medicine had led me to conclude that specialists often saw my troubles through their particular lens—an autoimmune disease! a viral issue! your mind! And I worried that if I were to go see a Lyme specialist—an internist with a focus on the disease—he would say I had it no matter what.

In the absence of medical clarity, I had to decide what to do. Was I going to become a Lyme patient? If so, whom was I to trust, and how far would I go? Then one night, in my rabbit-hole searching, I stumbled on a thread of Lyme patients describing the same electric shocks that had bedeviled me for years. The back of my neck went cold. For nearly 20 years I had tried to find a doctor who would think the problem was something other than dry skin. I had asked friends if they had any idea what I was talking about. No one ever did. I had thought I was imagining it, or being oversensitive—or was somehow at fault. To see my ordeal described in familiar, torturous detail jolted me to attention.

I knew then that I needed to learn more about the complex reality of Lyme disease and tackle the near-impossible task of sorting out what was understood and what wasn't. I didn't yet know that simply by exploring whether untreated Lyme disease could be the cause of my illness, I risked being labeled one of the "Lyme loonies"—patients who believed that a long-ago bite from a tick was the cause of their years of suffering. They'd been called that in a 2007 email sent by the program officer overseeing Lyme grants at the National Institutes of Health. The now-infamous phrase betrayed just how fiercely contested the disease is—"one of the biggest controversies that medicine has seen," as John Aucott, a physician and the director of the Johns Hopkins Lyme Disease Clinical Research Center, later described it to me.

Lyme Disease was discovered in Connecticut in the mid-1970s. Today it is a major, and growing, health threat, whose reach extends well beyond its initial East Coast locus. Reported cases increased almost fivefold from 1992 to 2017, and the Centers for Disease Control and Prevention estimates that annual incidences have risen to more than 300,000, and may even range above 400,000. Step into parks in coastal Maine or Paris, and you'll see ominous signs in black and red type warning of the presence of ticks causing Lyme disease. In the summer in the eastern United States, many parents I know cover their children from head to toe—never mind the heat—for a hike in the woods or a jaunt to a grassy playground. On a recent trip to my brother's new country house in Vermont, a few weeks before his partner woke up one morning with a dramatic bull's-eye rash, I chased my toddler sons around, spraying them so often with tick repellent that they thought we were playing a special outdoor game.

Read: What tick saliva does to the human body

By now, just about everyone knows someone who's been diagnosed with Lyme disease, and most of us know to look for the telltale rash (often described as a bull's-eye, many Lyme rashes are solid-colored lesions) and to ask for a prompt dose of antibiotics. For most of those who get swiftly diagnosed and treated, that will be the end of the story. But lots of Americans have also heard secondhand reports of people who stayed sick after that course of antibiotics. And lots know of cases in which no rash appeared and a diagnosis came late, when damage had already been wrought. Plenty of others, upon discovering an attached deer tick, have encountered doctors who balk at prescribing antibiotics to treat a possible Lyme infection, wary of overdiagnosis.

Reported Cases of Lyme Disease in the United States, by Year

(CDC data for Massachusetts are not available for 2016 and 2017.)

The degree of alarm and confusion about such a long-standing public-health issue is extraordinary. The consequences can't be overestimated, now that Lyme disease has become an almost "unparalleled threat to regular American life," as Bennett Nemser, a former Columbia University epidemiologist who manages

the Cohen Lyme and Tickborne Disease Initiative at the Steven & Alexandra Cohen Foundation, characterized it to me. “Really anyone—regardless of age, gender, political interest, affluence—can touch a piece of grass and get a tick on them.”

Even as changes in the climate and in land use are causing a dramatic rise in Lyme and other tick-borne diseases, the American medical establishment remains entrenched in a struggle over who can be said to have Lyme disease and whether it can become chronic—and if so, why. The standoff has impeded research that could help break the logjam and clarify how a wily bacterium, and the co-infections that can come with it, can affect human bodies. After 40 years in the public-health spotlight, Lyme disease still can’t be prevented by a vaccine; eludes reliable testing; and continues to pit patients against doctors, and researchers against one another. When I got my inconclusive diagnosis, I knew better than to dream of a quick cure. But I didn’t know how extreme the roller coaster of uncertainty would be.

Lyme Disease came into public view when an epidemic of what appeared to be rheumatoid arthritis began afflicting children in Lyme, Connecticut. A young rheumatologist at Yale named Allen Steere, who now conducts research at Massachusetts General Hospital, in Boston, studied the children. In 1976 he named the mysterious illness after its locale and described its main symptoms more fully: a bull’s-eye rash; fevers and aches; Bell’s palsy, or partial paralysis of the face, and other neurological issues; and rheumatological manifestations such as swelling of the knees. After much study, Steere realized that the black-legged ticks that live on mice and deer (among other mammals) might be harboring a pathogen responsible for the outbreak. In 1981, the medical entomologist Willy Burgdorfer finally identified the bacterium that causes Lyme, and it was named after him: *Borrelia burgdorferi*.

B. burgdorferi is a corkscrew-shaped bacterium known as a spirochete that can burrow deep into its host’s tissue, causing damage as it goes and, in laboratory conditions at least, morphing as needed from corkscrew to cystlike blob to, potentially, slimy “biofilm” forms. Because of this ability, researchers describe it as an “immune evader.” Once it hits the human bloodstream, it changes its outer surface to elude an immune response, and then quickly moves from the blood into tissue, which poses problems for early detection. (Hard to find in the bloodstream and other body fluids, the *B. burgdorferi* spirochete is hard to culture, which is how bacterial infections are definitively diagnosed.) If it goes untreated, *B. burgdorferi* can make its way into fluid in the joints, into the spinal cord, and even into the brain and the heart, where it can cause the sometimes deadly Lyme carditis.

By the mid-’90s, a mainstream consensus emerged that Lyme disease was relatively easy to diagnose—thanks to the telltale rash and flulike symptoms—and to treat. Infectious diseases are the kind of clear-cut illness that our medical system generally excels at handling. Evidence indicated that the prescribed treatment protocol—a few weeks of oral antibiotics, typically doxycycline—would take care of most cases that were caught early, while late-stage cases of Lyme disease might require intravenous antibiotics for up to a month. That assessment, made by the Infectious Diseases Society of America, formed the basis of the IDSA’s treatment guidelines from 2006 until recently. (In late June, a revised draft called for, among other things, a shorter course—10 days—of doxycycline for patients with early Lyme.)

Yet the picture on the ground looked far murkier. A significant percentage of people who had Lyme symptoms and later tested positive for the disease had never gotten the rash. Others had many characteristic symptoms but tested negative for the infection, and entered treatment anyway. Most startling, a portion of patients who had been promptly and conclusively diagnosed with Lyme disease and treated with the standard course of doxycycline didn’t really get better. When people from each of these groups failed to recover fully, they began referring to their condition as “chronic Lyme disease,” believing in some cases that the bacterium was still lurking deep in their bodies.

Frustrated with the medical system's seeming inability to help them, patients emerged as an activist force, arguing that Lyme disease was harder to cure than the establishment acknowledged. Family physicians in Lyme-endemic areas, confronted with patients who weren't getting better, tried out other treatment protocols, including long-term oral and intravenous antibiotics, sometimes administered for months or years. They also started testing assiduously for tick-borne co-infections, which were appearing in some of the sickest patients. Many of these doctors rotated drugs in the hope of finding a more effective regimen. Some patients responded well. Others didn't get better. In 1999, these doctors banded together to form the International Lyme and Associated Diseases Society. Highlighting the problems with Lyme-disease tests and citing early evidence that bacteria could persist in animals and humans with Lyme disease even after they'd been treated, ILADS proposed an alternative standard of care that defined the illness more broadly and allowed for more extensive treatment.

Jon Lovette / Getty

But some prominent Lyme-disease researchers were skeptical that the infection could persist after treatment—that bacteria could remain in the body. They argued that many chronic Lyme-disease patients were being treated for an infection they no longer had, while others had never had Lyme disease in the first place but had appropriated the diagnosis for symptoms that could easily have other causes. Chronic Lyme disease, in the Infectious Diseases Society of America's view, was a pseudoscientific diagnosis—an ideology rather than a biological reality. Under the sway of that ideology, it contended, credulous patients were needlessly being treated with dangerous IV antibiotics by irresponsible physicians. (It didn't help when a Lyme patient in her 30s died from an IV-related infection.)

To make its case, the IDSA cited a handful of studies indicating that long-term antibiotic treatment of patients with ongoing symptoms was no more effective than a placebo—proof, in its view, that the bacterium wasn't causing the symptoms. The IDSA also highlighted statistics suggesting that the commonly cited chronic Lyme symptoms—ongoing fatigue, brain fog, joint pain—occurred no more frequently in Lyme patients than in the general population. In the press, experts in this camp implied that patients who believed they had been sick with Lyme disease for years were deluded or mentally ill.

The antagonism was "fierce and alienating for the patients," Brian Fallon, the director of the Lyme and Tick-Borne Diseases Research Center at Columbia University Irving Medical Center, told me. Hostilities continued to intensify, not just between patients and experts, but between community doctors and academic doctors. In 2006, the IDSA guidelines for patients and physicians argued that "in many patients, posttreatment symptoms appear to be more related to the aches and pains of daily living rather than to either Lyme disease or a tick-borne co-infection." This message rang hollow for many. "Researchers were

saying, 'Your symptoms have nothing to do with Lyme. You have chronic fatigue syndrome, or fibromyalgia, or depression,' " Fallon told me. "And that didn't make sense to these patients, who were well until they got Lyme, and then were sick."

By the time the doctor first floated the possibility, in 2013, that I might have Lyme, my headaches, brain fog, and joint pain had gotten much worse, and tiny bruises had bloomed all over my legs and arms. I was so dizzy that I began fainting. A black ocean, it seemed, kept crashing over me, so that I couldn't catch my breath. I could no more touch the old delights of my life than a firefly could touch the world beyond the jar in which it had been caught.

When I returned to the doctor's office two weeks later to go over the test results, I didn't know what I was in for. Imperfect diagnostics lie at the core of the whole debate over Lyme disease. Standard Lyme tests —structured in two tiers, to minimize false positives—can't reliably identify an infection early on or determine whether an infection has been eradicated. That's because the tests are not looking for the "immune evader" itself—the *B. burgdorferi* spirochete—in your blood. Instead, they assess indirectly: They look for the antibodies (the small proteins our bodies create to fight infection) produced in response to the bacteria. But antibody production takes time, which means early detection can be hard. And once produced, antibodies can last for years, which makes it difficult to see whether an infection is resolved, or even whether a new one has occurred. What's more, antibodies to autoimmune and viral diseases can look like the ones the body makes in response to Lyme.

For a thorough interpretive reading, some doctors will send blood to several different labs, which can deliver results that don't always agree with one another. And the CDC—which recommends that only a specific pattern of antibodies, agreed on by experts in 1994, be considered indicative of a positive test—suggests that, when needed, doctors should use their judgment to make what's called a "clinical diagnosis," based on symptoms and likelihood of exposure, along with the lab tests.

I was confused. My doctor showed me mixed results from three labs. Two had a positive response on one part of the test but not the other, while the third had a negative response on both parts. Because of my medical history as well as particular findings on my tests, she concluded that I probably did have Lyme disease. But she also noted that I had a few nasty viruses, including Epstein-Barr. In addition, the test may have been picking up on autoimmune antibodies, given my earlier diagnosis.

At the recommendation of a science-writer friend, I finally went to seeRichard Horowitz, a doctor in upstate New York who specializes in Lyme disease and had earned a reputation as a brilliant diagnostician. Horowitz, who goes by "Dr. H" with many of his patients, is a practicing Buddhist, with bright-blue eyes and an air of brimming eagerness. He recently served as a member of the Tick-Borne Disease Working Group convened by the Department of Health and Human Services, which in 2018 issued a report to Congress outlining problems with the diagnosis and treatment of Lyme patients.

I told him that I wasn't sure I had Lyme disease. I had brought along a stack of lab results nearly half a foot tall—a paper trail that would scare off many doctors. He perused every page, asking questions and making notes. Finally, he looked up.

"Based on your labs, your symptoms, and your various results over the years, I highly suspect you have Lyme," he said. "See these?"—he bent over a set of results from Stony Brook laboratory—"these bands are specific for Lyme."

In his waiting room, I had completed an elaborate questionnaire designed to single out Lyme patients from a pool of patients with other illnesses that affect multiple biological systems. (It has since been empirically validated as a screening tool.) Now Dr. H did a physical exam and ordered a range of tests to rule out further thyroid problems, diabetes, and other possible causes of my symptoms. Because I had night sweats and the sensation that I couldn't get enough air into my lungs—a symptom known as "air hunger"—he proposed that I might have a co-infection of babesia, a malaria-like parasite also transmitted by ticks. Curious, I told him that I had always thought of Lyme as a primarily arthritic disease, whereas I had many neurological and cognitive symptoms. He explained that *B. burgdorferi* is now known to come in different strains, which are thought to produce different kinds of disease.

"The funny thing is, I think you're actually a very strong and healthy person, and that's why you did okay for so long," he continued. "Now your body needs help."

Douglas Sacha / Getty

Dr. H prescribed a month of doxycycline, and warned me about something I'd read online. When I began the antibiotic, I might at first feel worse: As the bacteria die, they release toxins that create what's known as a Jarisch-Herxheimer reaction—a flulike response that Lyme patients commonly refer to as "herxing." But over time, he said, I should feel better. If not, we were on the wrong track.

Over dinner that night, back in Brooklyn, I told Jim that despite what Horowitz had urged, I wasn't sure I wanted to take the antibiotics. I didn't have a cut-and-dried positive test for Lyme, and I knew how damaging antibiotics are to the microbiome. "What do you really have to lose?" he asked, in disbelief. "You're sick, you're suffering, and you've tried everything else."

The next morning, I took a dose of the doxycycline, along with Plaquenil, which is thought to help the antibiotics penetrate cells better. I took another dose that night with dinner. I went to bed and woke up feeling like hell. My throat was sore and my head was foggy. My neck was a fiery rebar.

Two days later, we went out to get lunch. I was still groggy and unwell. It was a heavy, gray day, with low clouds. Returning home, I felt rain all over my bare arms. I told Jim we should hurry.

"Why?" he said.

"It's raining!"

“It’s not raining,” he said. “It’s just cloudy.” I raised my hands to show him the raindrops. A dozen pips of cold popped along my arm. But there was no rain. As we walked home, cold drops rushed all over my body, my skin crawling as if a strange, violent water were cleansing it.

Several days later, though, I felt excited to fly to a conference in Chicago, rather than exhausted by the prospect. For three more weeks, I took the drugs and supplements Dr. H had prescribed. The doxycycline made me allergic to the sun. One late-spring morning, I forgot to put sunblock on my right hand before taking a walk with a friend, holding a coffee cup. It was 9 o’clock and cloudy. By the time I got home, my hand felt tender. Over the next few days a second-degree burn developed, blistering into an open wound.

After a month of antibiotic treatment, I took the train back up to Dr. H’s office. On his questionnaire, I rated my symptoms as less severe than I had a month earlier, but my total score still fell in the high range. Dr. H changed the protocol, adding an antimalarial drug. He was concerned about my continued night sweats and air hunger.

When I started taking the new drugs, in June 2014, I was nearly as sick as I had ever been. I flew to Paris to teach at NYU’s summer writing program. Within two days of arriving, I could barely walk down the street. Violent electric shocks lacerated my skin, and patches of burning pain and numbness spread up my neck. I shook and shivered. The reaction lasted five days, during which panic mixed with the pain. How was I to know whether this was herxing and a *positive* reaction to the drugs as they killed bacteria and parasites, or a manifestation of the disease itself? Or were weeks of antibiotics themselves causing problems for me?

“I know you think you’re doing the right thing,” a concerned colleague said, “but aren’t you just making yourself sicker?”

On the sixth day, I was sitting on the couch in my rented apartment and the shocks were so violent, racing across my forearms and thighs and calves, that when I looked up at the tall open windows, the sun streaming through them, it occurred to me that I could jump out of them and find relief.

The next morning I woke up to the same bright sun, feeling better than I had in ages. Stunned by my energy, I went out for a run. I wasn’t exactly racing down the sidewalk, but 40 minutes later, for the first time in years, I had run three miles. As the weeks passed, I felt better and better. My drenching night sweats vanished. The air hunger was gone. I had loads of energy. I took antibiotics for several more months, and each month I had fewer symptoms. After eight months of treatment, Dr. H decided that I could stop. It was the spring of 2015.

That fall I got pregnant, at the age of 39. At Dr. H’s urging, I took antibiotics on and off during my pregnancy. In the summer of 2016, I delivered a healthy baby boy.

By the time I started treatment, the fact that Lyme disease causes ongoing symptoms in some patients could no longer be viewed as the product of their imaginations. A well-designed longitudinal study by John Aucott at Johns Hopkins showed the presence of persistent brain fog, joint pain, and related issues in approximately 10 percent of even an ideally treated population—patients who got the Lyme rash and took the recommended antibiotics. Other studies found these symptoms in up to 20 percent of patients. The condition, christened “post-treatment Lyme disease syndrome,” or PTLDS, is now recognized by the CDC. (Of course, the term doesn’t apply to patients like me, who never had a rash or a clearly positive test.) Even so, the condition is hotly contested, and plenty of high-level people in the field—as well as the Infectious

Diseases Society of America itself—still don't recognize it as an official diagnosis. Perhaps most important, crucial questions about the cause of ongoing symptoms remain unanswered, due in part to the decades-long standoff over whether and how the disease can become chronic. As Sue Visser, the CDC's associate director for policy in the Division of Vector-Borne Diseases, acknowledges, "Many are very rightfully frustrated that it's been decades and we still don't have answers for some patients."

Recently, though, a host of new studies has freshly tackled a lot of those questions: Why do Lyme symptoms persist in only some patients? What don't we know about the behavior of the *B. burgdorferi* bacteria that might help explain the variation in patients' responses to it?

There isn't much federal funding to study Lyme disease, and what there is often goes to research on prevention and transmission. (The NIH spends only $768 on each new confirmed case of Lyme, compared with $36,063 on each new case of hepatitis C.) Much of the money to investigate PTLDS has come from private foundations, including the Steven & Alexandra Cohen Foundation, the Global Lyme Alliance, and the Bay Area Lyme Foundation. The CDC and the NIH recently reached out to these groups, officials told me, spurred on in part by the 2018 Tick-Borne Disease Working Group report to Congress outlining major holes in the scientific understanding of Lyme disease.

Read: When evidence says no, but doctors say yes

In a conversation I had with him, Bennett Nemser of the Cohen Foundation laid out some of the hypotheses that are currently being explored. The complexity is daunting. A patient with ongoing symptoms may actually still have a Lyme infection, and/or a lingering infection from some other tick-borne disease. Or the original infection might have caused systemic damage, leaving a patient with recurring symptoms such as nerve pain and chronic inflammation. Or the Lyme infection might have triggered an autoimmune response, in which the immune system starts attacking the body's own tissues and organs. Or a patient might be suffering from some combination of all three, complicated by triggers that researchers have not yet identified.

One way or another, an intricate interplay of the infection and the immune system, new research suggests, is at work in patients who don't get better. The immune response to the Lyme infection, it turns out, is "highly variable," John Aucott told me. For example, some research has suggested that ongoing symptoms are a result of an overactive immune response triggered by Lyme disease. Recently, though, a study co-authored by Aucott with scientists at Stanford found that, in patients who developed PTLDS, the Lyme bacteria had actually inhibited the immune response.

By now, accumulating evidence suggests that in many mammals, Lyme bacteria can persist after treatment with antibiotics—leading more scientists to wonder if the bacteria can do the same in humans. In 2012, a team led by the microbiologist Monica Embers of the Tulane National Primate Research Center found intact *B. burgdorferi* lingering for months in rhesus macaques after treatment. Embers also reported that the macaques had varying immune responses to the infection, possibly explaining why active bacteria remained in some. The study drew criticism from figures in the IDSA establishment; in their view it failed to prove that the bacteria remained biologically active. But Embers told me that this year, in their work with mice, she and her team have managed the feat of culturing *B. burgdorferi*, showing that it was viable after a course of doxycycline. New studies looking into possible bacterial persistence in humans—conducted by the National Institute of Allergy and Infectious Diseases, part of the NIH—are under way.

Markus Spiske / Unsplash

Meanwhile, several researchers, including Ying Zhang at the Johns Hopkins Bloomberg School of Public Health, have proposed another explanation for how *B. burgdorferi* can remain after treatment: the presence of what are called "persister bacteria," similar to those found in certain hard-to-treat staph infections but long thought not to exist in Lyme. In the case of Lyme disease, persister bacteria are a subpopulation that enters a dormant state, allowing them to survive a normally lethal siege of antibiotics. These persister bacteria, Zhang's team found, caused severe symptoms in mice, and the current single-antibiotic Lyme protocols didn't eradicate them—which makes sense: Doxycycline functions not by directly killing bacteria, but by inhibiting their replication. Thus it affects only actively dividing bacteria, not dormant ones, relying on a healthy immune system to dispatch any *B. burgdorferi* that remain.

The big outcome, though, was that when Zhang's teamtreated the mice with a three-antibiotic cocktail, including a drug known to work on persistent staph infections, the mice cleared the persistent *B. burgdorferi* infection. "We now have not only a plausible explanation but also a potential solution for patients who suffer from persistent Lyme-disease symptoms despite standard single-antibiotic treatment," Zhang said. Taking the next step, Kim Lewis at Northeastern University, who has had a distinguished career studying persister bacteria, is about to conduct a study, in collaboration with Brian Fallon, looking at whether a compound that specifically targets persister cells can help patients with PTLDS.

Of course, even if active bacteria do remain in some Lyme patients, they may well not be the cause of the symptoms, as many in the IDSA have long contended. Paul Auwaerter, the clinical director of infectious diseases at Johns Hopkins School of Medicine and a former president of the IDSA, points out that Lyme bacteria can leave behind DNA "debris" that may trigger ongoing "low-grade inflammatory responses." Lewis told me that the overarching question—"whether the pathogen is there and is slowly causing damage, or has already left the body and has wrecked the immune system"—has yet to be settled, in his view. But, he said, "I'm optimistic that we and others are going to find a cure for PTLDS."

When my son was seven months old, my interlude of feeling energetic and mostly symptom-free abruptly ended. He was not a good sleeper, and months of waking at night had worn me down. In early April 2017, we both got sick, and I didn't recover. My body ached. My brain got foggy. My primary-care doctor noted

that the Epstein-Barr virus was active in my system again. Dr. H suggested that the Lyme infection had recurred, and that I needed another course of antibiotics, but I hesitated. I wasn't sure whether to believe that the Lyme infection could persist, and I attributed my ill health to an autoimmune flare or postviral fatigue. For months I stalled, but soon the electric shocks were back, zapping my arms and legs, and life became a slog. I started antibiotics. Within five days, my energy returned and I felt almost completely well again. A month later, feeling better than I had in almost 20 years, I got pregnant with my second son.

Could this recovery be attributed to the placebo effect?, I wondered. If so, it was the only placebo that had ever worked for me.

Meanwhile, my father, who lived in Connecticut, had begun to suffer drenching night sweats, fatigue, and aches and pains. His tests were negative for Lyme but suggestive of ehrlichiosis, another tick-borne infection, and his doctor—in the heart of Lyme country—decided to treat what seemed like a plausible culprit and its co-infection. My father was put on doxycycline for five months. He didn't improve, which surprised me, given that I had seen immediate results. Then one day my brother found him at home, on the verge of collapse, and took him to an ER, where batteries of tests revealed that he had a different problem. He was suffering from Stage 4 Hodgkin's lymphoma.

In 2018, my father died of complications from pneumonia, after recovering from the cancer. I couldn't help wondering how much those lost months had perhaps cost him, as the cancer advanced and weakened him—all because Lyme had seemed like an obvious enough explanation, and the testing was sufficiently murky, that his doctor did not pursue other diagnoses. Though promising new diagnostic technologies are on the horizon, we still can't reliably sort out who has a tick-borne disease and who doesn't.

On a brisk March day this year, the kind of day that can't decide whether it's warm or cold, I visited a research laboratory at Massachusetts General Hospital directed by Allen Steere, the rheumatologist who discovered Lyme disease and helped establish the testing parameters for it. A slim, gray-haired man with an intense gaze, he has become, in the eyes of many Lyme patients, an embodiment of the medical system's indifference, because he has long suggested that some chronic Lyme patients were incorrectly diagnosed in the first place. He has been shouted down at conferences and ambushed by people purporting to be journalistic interviewers. Scientists who disagree with him had nonetheless singled him out to me for his commitment to studying Lyme. I wanted to hear his perspective on the disease and on the debate after four decades of immersion in both.

While underscoring that medicine can be humbling, and that Lyme disease is complex, Steere spoke with the calm air of someone setting a child straight. Emphasizing that in many people Lyme disease can resolve on its own without antibiotics, he carefully described a disease that in the United States frequently follows a specific progression of stages if untreated, beginning with an early rash and fever, then neurological symptoms, and culminating later in inflammatory arthritis. The joint inflammation can continue for months or even years after antibiotic treatment, but not, he believes, because the bacteria persist. His research on patients who have these continuing arthritis symptoms has revealed one cause to be a genetic susceptibility to an ongoing inflammatory response. This discovery has led to effective treatment for the longer-term challenges of Lyme arthritis, using what are called disease-modifying anti-rheumatic agents.

After I told him a little about my case, he struck a note of similarly solicitous firmness. He told me that in his view, late-stage Lyme (which is what I had been diagnosed with) usually does not cause a lot of "systemic symptoms," such as the fatigue and brain fog I had experienced. "I want you to free yourself

from the Lyme ideology," he said. "You clearly were helped by antibiotic therapy. But I don't favor the idea that it was spirochetal infection. Of course, there are other infectious agents," he continued, noting that some of them trigger complex immune responses.

Jon Tyson / Unsplash

I left Steere's office unnerved, thinking that if I had met a doctor with some version of this view in 2014, I would never have started doxycycline and gotten better. Could it really be that I had some condition other than Lyme that turned out to respond to antibiotics? He was an expert who had devoted his entire career to studying the mechanics of the disease; I was a patient who happens to be temperamentally both exacting and excitable, and scientifically curious—a layperson craving evidence.

That night I curled up with my computer in my hotel room and reread a 1976 *New York Times* article about the discovery of Lyme. New things struck me, in particular Steere's growing suspicion back then that bacteria couldn't be the cause, because this microorganism wasn't *acting* like a bacterium:

> The bacterial infections that are known to cause arthritis leave permanent joint damage, and bacteria are easy to see in body fluids and easy to grow in test tubes. Every effort to culture bacteria from fluids and tissues from the patients has failed.

Steere had moved on to a new possibility: "A virus is the most likely candidate," he told the *Times*. "Just because we haven't found one yet doesn't mean it isn't there. We'll keep looking." When I recently wrote to ask him if he had been "fooled" by Lyme disease back in the 1970s, he reminded me of how much he and others *had* learned, in just a few years, about this then-new infection. He went on to remind me that science can "lead to one 'dead end' after another. One needs to learn from these dead ends and continue trying."

“Anyone who says they really understand the pathophysiology of what’s going on is oversimplifying to some degree,” said Ramzi Asfour, a physician and member of the Infectious Diseases Society of America with notably open views on Lyme disease, when I reached him on the phone in his Bay Area office. Asfour has found that a one-size-fits-all approach to Lyme diagnosis and treatment is inadequate for most patients in his medical practice. We don’t know enough yet about diseases that are characterized by abnormal activity of the immune system, he emphasized. But, alongside the usual standardized protocols, they clearly call for the tactics of personalized medicine, because the immune system is so complex—and so individualized. For example, autoimmune diseases can be triggered by stressors that include trauma or infection. And standard lab reports don’t always capture early stages of disease. Listening to patients is crucial.

“Being an infectious-disease doctor is usually pretty rewarding in the conventional sense,” Asfour said. “The patient is in the ICU; you grow a bacteria, and you see it; then you give them a magic pill. They get better and walk home. It’s very satisfying.” The experience of Lyme patients challenges that model. As the surgeon Atul Gawande once wrote of the medical profession, “Nothing is more threatening to who you think you are than a patient with a problem you cannot solve.”

The less we understand about a disease, as Susan Sontag argued years ago in *Illness as Metaphor*, the more we tend to psychologize or stigmatize it. In the midst of the current debate over Lyme, I can’t help thinking about other illnesses that modern medicine misunderstood for years. Multiple sclerosis was once called hysterical paralysis, and ulcers were considered “a disease of tense, nervous persons who live a strenuous and worrisome life,” as one mid-century medical manual put it, outlining a notion that remained common until the 1980s. In fact, ulcers are caused by bacteria—though when a researcher proposed as much in 1983, he was almost literally laughed out of a room of experts, who swore by the medical tenet that the stomach was a sterile environment. Doctors now also know that not everyone with the bacteria gets an ulcer—it’s caused by a complex interplay of pathogen and host, of soil and seed, perhaps like post-treatment Lyme disease syndrome.

It is true that *Lyme disease* has become a term that stands for more than itself. If not an ideology, it is a metonym for all tick-borne illness, for embattled suffering, for the ways that medicine has fallen short of its promised goal of doing no harm—in this case by dismissing and mocking suffering patients. As Wendy Adams of the Bay Area Lyme Foundation put it to me, “We now have incontrovertible data that says these people are legitimately sick.” Just because a symptom is common and subjective—as fatigue is—doesn’t mean that a patient can’t tell the difference between a normal version of it and a pathological one. After all, we’re able to distinguish between the common cold and a case of the flu. When I was very ill, I felt like a zombie—more important, I felt categorically different from myself. By contrast, today I have aches and pains, and I’m tired, but I am more or less “me.”

Recently, I called Richard Horowitz and several other Lyme experts to ask them, once again, if they really thought it was likely that I had Lyme. “Meghan. You *have* Lyme disease,” Dr. H said. “You have had multiple Lyme-specific antibodies show up on your tests. You had all the symptoms that led to a clinical diagnosis. *And* you got better when you took antibiotics.” Others echoed his conclusion.

I live in uncertainties, as the poet John Keats put it while he was dying of an infection then thought to be a disease of sensitive souls, which we now know is tuberculosis. But I am fairly sure of one thing. In a week, or a month, or six months, I will start feeling less well. My head will get foggier, my energy level will sink. When I wake in the morning, I will have a severe headache. Sharp electric shocks will start running along my legs and arms, for minutes, then hours, then days. My older son will stop eating his breakfast as I twitch in pain, and say, "What's wrong, Mommy?" And once again I will ask Dr. H for antibiotics.

While writing this article, it happened. I took the antibiotics. I felt worse, and then I felt dramatically better. In a few months, when I have stopped nursing my younger son, I will try Dr. H's new anti-persister regimen. Consisting of three different drugs, including antibiotics used to treat persister bacteria found in diseases like TB and leprosy, it has put some of his most challenging patients into remission for nearly two years now.

I can't know for sure that I have Lyme disease. But to imagine that I might never have found the treatment that has saved my life in every sense—restoring its joy—terrifies me. I think often about patients who are less fortunate, whose disease, whatever it may be, has gone unrecognized. One of the bitterest aspects of my illness has been this: Not only did I suffer from a disease, but I suffered at the hands of a medical establishment that discredited my testimony and—simply because of my search for answers, and my own lived experiences—wrote me off as a loon. In the throes of illness, cut off from the life you once lived, fearing that your future has been filched, what do you have but the act of witness? *This is what it is like. Please listen, so that one day you might be able to help.*

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